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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,382	04/14/2004	Chih-Ping Liu	55600-8014.US01	8686

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,382	LIU ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 6/13/2007, including arguments/remarks and amended claims, was received on 10/12/2007 and has been entered into the record.

2. In the amendment received on 10/12/2007, the Applicants cancelled claims 6-13 and 15. Therefore, claims 1-5 and 14 are currently pending and are the subject of this office action.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Rejections withdrawn

Rejection of claims 1-5 and 14 under 35 USC § 112, first paragraph, regarding lack of enablement for a method of increasing the IL-10/IFN-γ ratio in a subject, comprising administration of IFN-τ until a desired clinical endpoint is achieved for any condition other than multiple sclerosis, as set forth on pages 4-5 of the office action mailed on 6/13/2007, is withdrawn in response to Applicants amendments to the claims to recite a method of increasing the IL-10/IFN-γ ratio in subject suffering from multiple sclerosis.

2. Rejections maintained

Claims 1-5 and 14 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for a method of increasing the IL-10/IFN-γ ratio in a subject, wherein said method comprises administration of any IFN-τ other than SEQ ID NO: 2 or 3, as set forth on pages 3-4 of the office action mailed on 6/13/2007 and pages 2-4 of the office action mailed on 12/4/2006.

In the response received on 10/12/2007, the Applicants note that the claims have been amended to recite IFN-τ having at least 90% homology to the polypeptide of SEQ ID NO: 2. Furthermore, the

Applicants argue that the claims require administration of polypeptides that are IFN-τ polypeptides, and that IFN-τ polypeptides were known in the art at the time of filing, as evidenced by Roberts *et al*, Radhakrishnan *et al*, and WO 94/10313. Specifically, the Applicants assert that these references provide several examples of IFN-τ genes and polypeptides and their derivatives, as well as structure/function relationships. Therefore, a person of ordinary skill in the art would have been able to practice a method increasing the IL-10/IFN-γ ratio by administering IFN-τ polypeptides that are at least 90% identical to SEQ ID NO: 2.

These arguments have been fully considered and are not persuasive. The breadth of the claims is excessive in that the claims, although now reciting polypeptides with 90% identity to SEQ ID NO: 2, read on a large number of IFN-τ polypeptides that may or may not be capable of stimulating an increase in the IL-10/IFN-γ ratio. Alexenko *et al* (*J. Interferon and Cytokine Res.*, 1999, Vol. 19, p. 1335-1341 – cited in the IDS received on 5/5/2004) teaches that IFN-τ variants have different biological effects. Alexenko *et al* tested a number of IFN-τ subtypes for biological activity (anti-viral activity) on bovine, murine, and human cells. The variants exhibited ranges of biological activities across species (Table 2). Data presented in Table 2 indicate that the more sites of substitution relative to OvIFN-tau4, the less relative anti-viral activity the molecule exhibited, and the less cross-species activity exhibited. Although the teaching of Alexenko *et al* is directed to anti-viral activity, one of ordinary skill in the art could reasonably predict that this would be true for other biological activities of IFN-τ as well, including the effect on the IL-10/IFNγ ratio. Thus, one of ordinary skill in the art would not be able to predict which of the many possible polypeptides having only 90% identity to SEQ ID NO: 2 would possess the ability to increase the IL-10/IFN-γ ratio in a subject with multiple sclerosis., and therefore a person of skill in the art would not be able to make and use all other possible IFN-τ polypeptides having only 90% identity to SEQ ID NO: 2 without further, undue experimentation.

Furthermore, although IFN-τ structure/function relationships have been studied, a skilled artisan would still not be able to predict the effect of extensive mutation or alteration of residues of the SEQ ID NO: 2 amino acid sequence to create a polypeptide having 90% identity to SEQ ID NO: 2. The positions within the polypeptide sequence where such amino acid substitutions or alterations can be made with a reasonable expectation of success are limited. Wells (*Biochemistry*, 1990, Vol. 29, p. 8509-8517) teaches that combinations of mutations may exhibit simple or complex additivity, depending on the sites of mutation (p. 8515, 2nd column, 3rd - 4th paragraphs). Thus, the more substitutions introduced into the sequence, the less likely one would create a protein which retains the desired biological activity. SEQ ID NO: 2 is a protein of 172 amino acids; a protein which is 90% identical would comprise substitution of 17

amino acids. Alexenko *et al* indicates that the more sites of substitution relative to the canonical OvIFN-tau4 sequence in a given variant, the less likely the resulting protein will retain the required functional activity. The OvIFN-tau1, which has 21 amino acid substitutions, retains only 13.6% of the functional activity of the canonical sequence in a bovine cell line, and has very low activity in mouse or human cell lines (Table 2). Bovine IFN-tau-1a, which has 33 amino acid substitutions relative to the canonical sequence, also retains just a fraction of the activity of OvIFN-tau4 (Table 4). The specification does not disclose which amino acids or regions of amino acids can be altered. Therefore, a person of ordinary skill in the art would require further, undue experimentation in order to make and use an IFN-τ polypeptide of only 90% identity to SEQ ID NO: 2 in a manner commensurate in scope with the claims.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 1-5 and 14 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of written description for the genus of IFN-τ polypeptides with only 90% identity to SEQ ID NO: 2 capable of increasing the IL-10/IFN-γ ratio in a patient suffering from multiple sclerosis, as set forth on pages 5-6 of the office action mailed on 6/13/2007.

In the response received on 10/12/2007, the Applicants argue that the claimed genus of IFN-τ polypeptides has been described in such a way as to reasonably convey to one of skill in the art that the Applicants had possession of the claimed genus because the specification and the art, as illustrated by Roberts *et al*, Radhakrishnan *et al*, and WO 94/10313), describes numerous IFN-τ polypeptides as well as structure/function relationships for said IFN-τ polypeptides. The Applicants also argue that the claims of the instant invention have been amended to recite administration of only IFN-τ polypeptides, wherein said IFN-τ polypeptides have at least 90% homology to the polypeptide of SEQ ID NO: 2. Therefore, the claimed genus of IFN-τ polypeptides with at least 90% homology to SEQ ID NO: 2 has been adequately described.

These arguments have been fully considered and are not persuasive. As discussed above, Alexenko *et al* teaches that different IFN-τ polypeptides vary in regards to biological activity. Neither the specification nor the art describes any IFN-τ polypeptide, other than SEQ ID NO: 2 or 3, which is capable of increasing the IL-10/IFN-γ ratio in a patient suffering from multiple sclerosis. Furthermore, neither the specification nor the art describes which amino acid of SEQ ID NO: 2 may be substituted or altered and still produce an IFN-τ polypeptide that is able to increase the IL-10/IFN-γ ratio. Thus, the claimed genus

of IFN-τ polypeptides that are 90% homologous to SEQ ID NO: 2 and still able to increase the IL-10/IFN-γ ratio in a patient suffering from multiple sclerosis has not been adequately described.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 14 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of Soos *et al*, van Boxel-Dezaire *et al*, and Petereit *et al*, as set forth on pages 6-8 of the office action mailed on 6/13/2007.

The claims of the instant invention are drawn to methods of increasing the IL-10/IFN-γ ratio in subjects suffering from multiple sclerosis, wherein said method comprises oral administration of IFN-τ at a daily dose of 5×10^8 units or greater. The claims are further drawn to administration of ovine or bovine IFN-t, and specifically that of SEQ ID NO: 2 or 3.

Soos *et al* teach oral administration of IFN-τ polypeptides for the treatment of multiple sclerosis (see abstract; p. 5, lines 8-21; p. 11, line 5 – p. 12, line 16, p. 23, Example 1; and all claims). Specifically, Soos *et al* teaches administration of IFN-τ defined by SEQ ID NO: 2, which exhibits 100% homology to the polypeptide defined by SEQ ID NO: 2 of the instant application (see sequence comparison 1 – previous office action). Soos *et al* also teaches that orally administered IFN-τ increases serum IL-10 levels (p. 26, Example 5), while promoting a decrease of IFN-γ blood levels (p. 2233-2234, Figure 2), thus resulting in an overall increase in the IL-10/IFN-γ ratio. Furthermore, Soos *et al* teaches combination therapies wherein IFN-τ is co-administered with other therapeutic agents effective for the treatment of multiple sclerosis (p. 20, line 19 – page 21, line 14). Soos *et al* is silent regarding oral administration of IFN-τ at doses of at least 5×10^8 units/day.

van Boxel-Dezaire *et al* teaches that multiple sclerosis is characterized by decreased IL-10 levels (see Figures 1-3), and suggests that IL-10 plays an important role in the control of disease progression. Petereit *et al* teach that multiple sclerosis patients with higher IL-10 secretion had lower clinical disability scores than patients with lower IL-10 secretion (see abstract and p. 211-212).

In the response received on 10/12/2007, the Applicants argue that none of the references, separately or in combination, teach orally administering IFN-τ to a subject at the claimed dosage of about 5 x 10^8 Units, and therefore the claimed subject mater is not obvious in view of the cited combination.

These arguments have been fully considered and are not persuasive. As set forth in the previous office action, Soos *et al* teaches oral administration of IFN-τ to subjects suffering from multiple sclerosis, and also discloses that oral administration of IFN-τ to multiple sclerosis patients results in an increase in the IL-10/IFN-γ ratio. Petereit *et al* and van Boxel-Dezaire *et al* show the relationship between IL-10 levels and disease progression, and suggest that increasing IL-10 levels in a patient may be therapeutically useful (see van Boxel-Dezaire). Thus, the combination of Soos *et al*, van Boxel-Dezaire *et al*, and Petereit *et al* provide the motivation, as well as a reasonable expectation of success, in treating a subject suffering from multiple sclerosis by oral administration of IFN-t.

Although the combination of Soos *et al*, van Boxel-Dezaire *et al*, and Petereit *et al* does not explicitly teach oral administration of IFN-τ at the claimed dosage of about 5 x 10^8 Units, it would be obvious to one of ordinary skill in the art to optimize the dosage because the claimed therapeutic agent (IFN-τ) has already been shown to be effective for treatment of multiple sclerosis. MPEP 2144.05 states:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

In the instant case, the general conditions of the claims, namely oral administration of IFN-τ to subjects suffering from multiple sclerosis, are disclosed or suggested in Soos *et al*, van Boxel-Dezaire *et al*, and Petereit *et al*. Furthermore, Soos *et al* teaches that administration of IFN-τ is advantageous in view of its lower toxicity compared to other IFNs, and can therefore be administered at higher doses than other IFNs. In the Applicants' response, the Applicants argue that this teaching is already reflected in the high dosages described in Soos *et al* (1 x 10^8 units/day), and is not an invitation to administer yet higher doses than already described. It is noted, however, that because Soos *et al* teaches lower toxicity of IFN-τ, and also because there is nothing in Soos *et al* which teaches away from administering higher doses, one of ordinary skill in the art would have further motivation to optimize the dosage of orally administered IFN-τ for the treatment of multiple sclerosis.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Rejection of claims 1, 3, and 4 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 17, and 18 of co-pending Application No. 11/112,369, as set forth on page 8 of the office action mailed on 6/13/2007, is *withdrawn* in response to Applicants' submission of a terminal disclaimer of co-pending Application No. 11/112,369.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner
Art Unit 1647